One to Two Year Treatment of Parkinson's Disease with Levodopa

LEO J. TRECIOKAS, M.D., ROBERT D. ANSEL, M.D., AND CHARLES H. MARKHAM, M.D., *Los Angeles*

■ *One hundred patients with Parkinson's disease were treated with levodopa for more than a year at UCLA Medical Center. They were examined at given intervals and their improvement was graded. The optimum therapeutic dose was attained by balancing side effects against relief of symptoms and ranged from 1.5 grams to 8.0 grams per day (average 4.3 grams). There is no doubt that levodopa is the most effective treatment now available for Parkinson's disease. At the end of the first year, 60 percent of the patients improved 50 percent or better, and 10 percent were considered symptom-free. All major symptoms of this disease, including rigidity, akinesia and tremor, improved in variable degree.*

There were no serious abnormalities in the routine clinical laboratory tests. The comon side effects included nausea, vomiting and choreoathetoid dyskinesias. The side effects were not life threatening, but occasionally were major therapeutic challenges.

Maximal benefits with minimal side effects were achieved only by careful adjustments of the levodopa dosage as the months went by. This needed careful management by the physician and cooperation by the patient. Anticholinergic medications or amantadine hydrochloride, sometimes both, usually supplemented the effect of the levodopa.

LEVODOPA (L-3,4-dihydroxyphenylalanine) can now be considered an established therapeutic agent for Parkinson's disease. In the decade it has taken to reach this stage, there have been at least five major episodes. (1) Dopamine was demonstrated in the mammalian central nervous system[1] and was shown to have the highest concentration in the striatum—the caudate nucleus and putamen.[2,3,4] (2) Dopamine concentration was much reduced in the striatum and substantia nigra in Parkinson's disease.[4] Furthermore, Barbeau et al, in 1961, showed reduction of dopamine in the urine of parkinsonian patients.[5] (3) Several groups of Swedish investigators whose closely interlocking work was reviewed by Hillarp, Fuxe and Dahlström in 1966, demonstrated by histofluorescent technique a nigrostriatal neuronal pathway containing dopamine.[6] (4) Birkmayer and Hornykiewicz first showed in 1961 that intravenous dopa caused a clear but transient improve-

From the Department of Neurology, University of California, Los Angeles, School of Medicine.

Submitted, revised, November 16, 1970.

Reprint requests to: Department of Neurology, University of California, Los Angeles, School of Medicine, Los Angeles, Ca. 90024 (Dr. C. H. Markham).

ment in parkinsonian akinesia.[7] Possibly because the effects were mild, and also because of scepticism of new drugs in the treatment of Parkinson's disease, later studies with intravenous or small (we would now say) oral doses of levodopa either gave weak confirmation or reported no significant effect. (5) Cotzias et al, in 1967, reported that DL dopa in doses of 3 to 16 grams a day produced major and occasionally complete remission of parkinsonian rigidity and akinesia.[8] They reported less effective control of tremor. These results were accompanied by significant side effects: leukopenia in 4 of 16 patients. When the levo-rotatory form was used alone in large doses, beneficial effects were still striking and were not complicated by potentially serious side effects.[9,10,11]

The present report is based on a clinical study conducted at the UCLA School of Medicine during the past two years. This series consists of the first 100 patients to enter our treatment program. The patients now have been followed for one year to two years. The purpose of this report is to describe the therapeutic effects, side effects and treatment failures of levodopa in Parkinson's disease.

Methods and Materials

The series consisted of 63 men and 37 women ranging in age from 40 to 78 years (average, 62). Ninety-two had Parkinson's disease (paralysis agitans) and seven were considered to have postencephalitic parkinsonism. One patient had an associated en plaque meningioma and his parkinsonism was considered to be atypical. Forty-three of the patients had had previous stereotactic surgical operation for their illness. The duration of the illness for the entire group ranged from 2 to 46 years (average: 10.7).

In the first ten patients we started the administration of levodopa in the hospital. Thereafter we initiated the levodopa therapy in the outpatient clinic. A pretreatment evaluation consisted of a complete history and general medical and neurological evaluation to confirm the diagnosis and rule out any serious illnesses. The laboratory evaluation included a complete blood count, urinalysis, liver function studies (bilirubin, SGOT, LDH), renal function test (BUN), PBI, uric acid, Coombs test, chest x-ray film and an electrocardiogram. For the first three months, follow-up visits and laboratory tests were obtained every two weeks. After an optimal dose of the drug was obtained, follow-up visits were at one- to two-month intervals.

In order to assess the improvement in patients taking levodopa, we used a two-part scoring system to quantitate the efficacy of the drug (Table 1).[11] The first part was a list of symptoms and signs. The second part was related to disability in performing various daily activities (bottom of Table 1). Answers to this part were obtained by questioning the patient. Each of the items in the two categories was then weighted on a 1 to 10 scale according to its importance and multiplied by a number related to the degree of severity of the symptom (0=absent, 1=present, 2=pronounced). This gave a possible maximum total score of 108 for the signs and symptoms and 112 points for functional disability. At each visit, the improvement was determined by taking the total score as calculated before therapy and subtracting a score at a given time, the remainder then being divided by the initial score to express the amount of improvement in percentage. For example, if a patient had an initial score of 90 and later it decreased to 40, then the remainder of 50 would be divided by the initial score of 90 and the improvement would be stated as 55.5 percent.

Anticholinergic agents were continued in those patients using them. After an optimal dose of levodopa was achieved, we attempted to discontinue these standard antiparkinsonian drugs.

At the beginning of the investigation we were excluded patients with various disabilities, such as hypertension or previous myocardial infarction. Later we included patients with diastolic pressure of less than 100 mm of mercury. A number had bundle branch block or previous compensated congestive heart failure. Patients with clinical evidence of active renal, endocrine, hepatic or pulmonary disease, malignant disease or psychosis were not accepted. We did not accept patients who were taking phenothiazines, thixanthines, butyrophenones, phenylpiperazines, reserpine, monoamine oxidase inhibitors, or alpha methyl dopa because these drugs also act on the catacholamines and serotonin. However, later we used, without problems, phenothiazines in small doses to control nausea, and amitriptyline hydrochloride (Elavil®), imipramine hydrochloride (Tofranil®) and protriptyline hydrochloride (Vivactil®) to combat depression. Since pyridoxine reverses the effects of levodopa, we instructed our

TABLE 1.—*Specimen Sheet Showing Scoring Factors Used in Determining Effect of Levodopa Therapy** (see text)

		Control Rating 0=absent 1=present 2=marked	*Rating at time of visit when taking levodopa 0=absent 1=present 2=marked*
Symptoms and signs			
Rigidity	(7)	× _____ = _____	× _____ = _____
Tremor	(5)	× _____ = _____	× _____ = _____
Akinesia	(9)	× _____ = _____	× _____ = _____
Dementia	(8)	× _____ = _____	× _____ = _____
Postural Abnormality	(3)	× _____ = _____	× _____ = _____
Depression	(5)	× _____ = _____	× _____ = _____
Seborrhea	(2)	× _____ = _____	× _____ = _____
Sialorrhea	(2)	× _____ = _____	× _____ = _____
Blepharospasm	(2)	× _____ = _____	× _____ = _____
Masked Facies	(1)	× _____ = _____	× _____ = _____
Speech	(10)	× _____ = _____	× _____ = _____
Activities			
Dressing	(5)	× _____ = _____	× _____ = _____
Eating	(7)	× _____ = _____	× _____ = _____
Walking	(10)	× _____ = _____	× _____ = _____
Getting Out of Bed	(6)	× _____ = _____	× _____ = _____
Turning in Bed	(4)	× _____ = _____	× _____ = _____
Getting Out of Chair	(5)	× _____ = _____	× _____ = _____
Climbing Stairs	(2)	× _____ = _____	× _____ = _____
Use of Toilet	(6)	× _____ = _____	× _____ = _____
Bathing	(6)	× _____ = _____	× _____ = _____
Handwriting	(5)	× _____ = _____	× _____ = _____
		Total Control Value: _____	Total Value at Time of Visit: _____

*Improvement was computed by the following mathematical formula:

$$\frac{\text{Total Control Value—Total Value at Time of Visit}}{\text{Total Control Value}} \times 100 = \text{Percent Improvement}$$

patients to avoid any vitamin supplement containing B_6 and also foods that contain large amounts of that vitamin—all beans and peas, sweet potatoes, yams, wheat germ, wheat bran, vitamin-enriched bread, bacon and pork, avocado, nuts and most of the so-called health foods.

We started administration of levodopa in a 500 mg dose daily and increased it by the same amount every fourth day until a daily dose of 3.0 grams was reached. From then on, increases were made very gradually and adjusted individually. The dosage increase was carried to the point of maximum benefit with regard to symptoms, or until significant side effects occurred, or until a dosage of 8.0 grams a day was reached. The daily dose was divided into four or as many as six allotments. Concurrently, patients were encouraged to engage on a course of physiotherapy suited to their individual needs.

Therapeutic Effects

First signs of improvement usually appeared after the second or third week of therapy. The patient himself often noted that he could turn in bed more easily or had less tendency to hesitate while walking. As measured by our previously mentioned scoring method, more than one-fourth of the patients had improved 50 percent or more by the end of the first trimester (Table 2). At the end of six months, more than half had improved 50 percent or better, and by the end of the first year this degree of improvement had been attained by 62 percent of all patients who had started in the treatment program. At the end of 12 months 10 percent of the group were considered to be free of symptoms. This figure remained unchanged as long as they continued to take the prescribed medication. Only three patients were lost to the program, one because of intractable nausea and vomiting at a dosage of 1 to 1.5 grams of levodopa a day, another who relapsed to his former incapacity after initial improvement, and a third who died of congestive heart failure unrelated to the treatment of Parkinson's disease. A few patients continued to improve after six months; a few regressed because of side effects and inability to take large doses of the drug.

TABLE 2.—*Degree of Improvement in Patients Receiving Levodopa Therapy*

Time of Exam	No. of Patients	Treatment Stopped*	Worsened	0-24 (percent)	25-49 (percent)	50-74 (percent)	75-99 (percent)	100 (percent)
3 months	100	0	1	31	31	19	16	2
6 months	100	1	0	15	27	25	22	10
12 months	100	3*	1	10	24	29	23	10

*Means the figure is cumulative from previous examination period.

TABLE 3.—*Percentage Improvement in Individual Signs, Symptoms and Daily Acts of Living*

	3 Months	6 Months	12 Months
Rigidity	45	66	62
Tremor	28	42	45
Akinesia	42	42	68
Dementia	29	48	51
Postural Abnorm.	13	33	55
Depression	53	52	58
Seborrhea	48	58	60
Sialorrhea	65	79	79
Blepharospasm	62	73	73
Masked Facies	43	53	74
Speech	33	40	47
Dressing	29	28	38
Eating	49	59	61
Walking	34	47	46
Out of Bed	36	60	60
Out of Chair	47	63	64
Stairs	39	50	51
Toilet	56	65	56
Bathing	32	47	49
Handwriting	26	44	52

Improvements in individual factors were variable. In evaluating three major signs and symptoms of Parkinson's disease we found that relief from rigidity was greatest early in the treatment, as shown in Table 3. At the end of the year, however akinesia was improved most (68 percent), rigidity next with 62 percent and tremor least with 45 percent.

The optimal daily dose represented a balance between limiting side effects, such as involuntary movements which developed at high levodopa doses, and maximum benefit as judged by the investigator. It ranged between 1.0 and 9.0 grams per day (average: 4.3). In individual patients, this optimal dose decreased or increased by one or two grams per day over the year. In some patients choreoathetosis developed (see below under side effects) and their daily dose had to be reduced; in others, improved tolerance permitted an increase.

We have also found that anticholinergic drugs were complimentary with levodopa in the treatment of Parkinson's disease. Before the initiation of therapy, 87 of our patients were taking anticholinergic drugs and five took amantadine hydrochloride. During the year, these drugs were discontinued two or three times and were started again only if the patient was clearly deriving some benefit from them. By the end of the first year, there were still 60 patients who continued taking one of the anticholinergic preparations. Most commonly the reason for this was that it was contributing to the reduction of tremor. Other patients who attempted to discontinue these drugs found moderate worsening of their other signs and symptoms. Similarly, in a few of the cases amantadine hydrochloride complimented the effectiveness of levodopa.

One of the factors which appeared to have an effect on the degree of improvement with levodopa was the severity of illness. This is brought out in Table 4. All patients who had 100 percent improvement came from the moderately impaired group and none from the severely affected group. The latter group also rated poorer in over-all improvement, since more than half did not achieve even a 50 percent improvement and it also included the only patient who became worse during the treatment. These criteria, however, do not measure the significant benefit in an individual. A patient who had been totally disabled and then became able to feed himself and walk with

TABLE 4.—*Severity of Parkinson's Disease and Improvement After 12 Months*

	Treatment Stopped	Worsened	0-24%	25-49%	50-74%	75-99%	100%
Mild	0	0	0	0	1	1	0
Moderate	1	0	6	13	18	16	10
Severe	2	1	4	11	10	6	10

TABLE 5.—*Side Effects*
(Severe side effects are given in parentheses)

	Duration of Therapy			
	3 Months	*6 Months*	*12 Months*	*Total*
Nausea and/or Vomiting	36(2)	18(1)	7(0)	43(3)
Anorexia	4	1	0	5
Postural Hypotension	7	2	2	9(0)
Flushing	0	0	0	0
Dyskinesias	21(2)	24(3)	8(2)	38(4)
Mental Disturbances	4	2	0	5
Organic Confusion	5	3	0	6
Cardiac Disturbances	4	2	0	4
Palpitation	4	2	0	4
Dysrhythmias	0	0	0	0

some difficulty may have improved less than 25 percent on our grading scale, yet to him these improvements were of considerable importance.

Other factors such as age, duration of illness, cause of disease, and previous stereotaxic brain operations did not influence the therapeutic effect of levodopa. On the other hand, the presence of organic dementia or of depression reduced the likelihood of pronounced improvement.

Side Effects

The incidence of side effects is listed in Table 5. These include nausea, vomiting, anorexia, involuntary movements, postural hypotension and cardiac disturbances. Nausea and vomiting most commonly occurred in the morning and were a problem at some stage in almost half of the patients. For the most part these symptoms subsided with time. One patient had to discontinue levodopa because of intractable nausea and vomiting. The incidence of nausea and vomiting could be reduced by slowing the rate of increase of levodopa, by taking the drug with food, or by dividing the daily dose into smaller amounts. Sometimes taking an antacid before the levodopa tablet helped. In several patients, a phenothiazine (Compazine®) was useful. We also tried to de-emphasize the side effects of nausea and vomiting in the patients mind, as we have observed that these symptoms can be due to placebo alone.

When higher doses were reached, some patients again had nausea and vomiting. Reducing the dosage by 0.5 or 1.0 grams usually controlled these symptoms. Anorexia, accompanied by some weight loss was seen in four patients early in the treatment and in one late in the treatment.

The involuntary movements, best characterized as choreoathetoid or dystonic, appeared in 38 patients. At the end of one year they were present in eight patients, severe in two. They consisted of undulating movement of the tongue, head-bobbing, mouthing movements and head-turning. Less commonly there were jerking movements of the arms or legs. In a few patients, rhythmic contractions of the thorax and abdomen made respirations shallow and rapid. These movements were often exaggerated by volitional movements of other parts of the body.

The involuntary movements sometimes appeared in the first few months of levodopa therapy, but sometimes not until the sixth to the twelfth month. They seemed to be characteristic of patients with Parkinson's disease, since they did not appear in six normal controls used early in the study or in patients with other movement disorders such as spasmotic torticollis or dystonia musculorum deformans. When abnormal movements occurred, they could usually be controlled by reducing the daily dose by 0.5 to 1.0 gram. Several patients benefited by a reduction in levodopa dosage and the addition of a phenothiazine or imipramine hydrochloride. However, two patients have been on a borderline between inadequate control of Parkinson's disease and incapacitating choreoathetosis.

Postural hypotension was defined as a drop in blood pressure of 30 mm of mercury on assuming an upright position or a fall of systolic blood pressure below 100 mm. It occurred in nine patients, some of whom complained of dizziness in upright posture. None of the patients fainted, although fainting has been reported by other investigators.[12] These patients were severely disabled with Parkinson's disease, particularly akinesia and rigidity, and most of them were depressed. The postural hypotension was reduced by either decreasing the levodopa a modest amount or by use of elastic stockings. It usually cleared after several months. We did not use fludrocortisone acetate (Florinef®) for hypotension although other investigators[11] have.

Mental disturbances, as found in five patients, consisted of insomnia, depression and euphoria. Depression usually predated the use of levodopa. These patients did not have any organic dementia. There were six other patients who exhibited clear organic mental disturbances, five early and one late. It persisted in two of them during the

TABLE 6.—*Comparison of Patients Considered Treatment Failures With Those With 100 Percent Improvement*

Pt.	Age	Sex	Duration of Illness	Disability Rating Before Rx	Percent Improved	Main Symptom	Optimum Levodopa Dose	Side Effects	
								Dyskinesia	Nausea or Vomiting
1	69	M	7	176	20	A	7.5	—	—
2	70	M	7	131	20	A	8.0	—	—
3	70	F	10	95	8	A;R;T	6.0	—	Moderate
4	61	F	9	121	18	A	3.0	Mild	Severe
5	62	M	7	102	22	A;R	7.0	—	—
6	68	M	9	113	9	A;T	5.5	—	Moderate
7	74	F	8	88	100	R	2.0	—	—
8	63	M	13	86	100	R;A;T	4.0	—	Mild
9	61	M	11	91	100	R;A;T	3.0	Mild	—
10	58	M	5	98	100	R;A;T	5.0	Mild	Mild
11	42	M	4	60	100	T	5.0	Mild	Mild
12	62	M	22	112	100	R;A;T	5.0	—	Mild
13	53	M	7	77	100	R;A;T	4.5	Mild	—
14	62	M	4	38	100	R;A	3.5	Mild	—
15	44	M	6	60	100	R;A	7.0	—	—
16	74	F	5	43	100	R;A	2.5	—	Mild

A=Akinesia. R=Rigidity. T=Tremor.

full year. In these cases, confusion, hallucinations and agitation were prominent. Most of these patients had some organic dementia before therapy. Depression was successfully treated by the usual recommended therapeutic doses of amitriptyline (Elavil®), imipramine (Tofranil®), or protriptyline (Vivactil®) while continuing the levodopa at previous dosage levels.

In none of the cases in our series did we note the cardiac dysrhythmia reported elsewhere,[10,11] although four patients have complained of heart palpitations, frequently occurring after ingestion of large doses of the drug.

Sexual performance improved only in relation to the improvement in mobility and well-being and no aphrodisiac effects were observed.

There was one death in our group. The cause was congestive heart failure and there was no evidence it was related to levodopa therapy.

There were few biochemical abnormalities observed. There were no instances of protein-bound iodine elevation. No leukocytosis or leukopenia were noted. Positive reaction to Coombs test developed in four patients during therapy, but no hemolytic abnormality was demonstrated. Transient BUN elevations with values from 22 to 35 were seen in 15 of the patients. Creatinine determinations remained normal. Degradation products of levodopa frequently resulted in change of urine color to deep amber, especially on standing, and also resulted in positive urine tests for acetone and diacetic acid. Serum transaminase elevation due to impaired gastrointestinal absorption or reflected in seven patients, but this also was transient and mild. Normocytic, normochromic anemia with hematocrits of 28 and 30 occurred in two patients, but no explanation for this could be found. None of these laboratory abnormalities necessitated reducing or discontinuing levodopa.

Discussion

The data we have presented is comparable to that of other reported series.[10,11] There were individuals who showed pronounced improvement, others who responded rather poorly. Comparing and contrasting some of the factors in Table 6 brings out some interesting features. It is apparent that those who had no symptoms at the end of the first year of treatment were relatively less disabled at the beginning of therapy. There was no difference in age or duration of illness between the two groups. However, the poorly responsive group of patients had severe akinesia as compared with other patients. The average levodopa dose for the group which responded poorly was much greater (5.1 grams) than for the entire study group or select symptom-free group (4.3 grams). Since all the patients had the levodopa dosage pushed to the point of significant side effects or to a level of 8 (or rarely 9) grams a day, this indicates these individuals were able to tolerate larger than usual amounts of the drug. One can perhaps speculate that those who responded poorly, despite high doses of levodopa, did so because their central dopamine levels were never high. This may be lated to transport across the blood brain barrier.

The efficacy of levodopa in Parkinson's disease based on one year's experience is unequivocal. It is the best treatment we have found for parkinsonism. Its clinical effect is due to, and has in turn produced considerable interest in monoamine research. At the same time, it is not an ideal medication. Its side effects, while not life-threatening, may be persistent and troublesome. The dosage administered is very high considering the small amount which is presumably active in the central nervous system.

Many questions remain. Does levodopa retard the progression of the disease by reducing the rate of dying of nerve cells in the substantia nigra which are responsible for dopamine production? Or does the large amount of therapeutically administered levodopa simply allow the remaining cells in the nigra to perform the dopa-to-dopamine decarboxylation more easily, while the gradual cell death goes on? There is some evidence to suggest that patients with virtual absence of nerve cells in the substantia nigra do not have therapeutic response to levodopa.[12] Clinical trials followed by post-mortem examinations for five to ten years will be necessary to resolve this issue.

The choreoathetoid dyskinesia induced by levodopa is a unique movement disorder and is also of interest. So far, we have seen it occur only in parkinsonian patients. It appears that an underlying cellular and biochemical alteration specific to these patients may be an important factor in these involuntary movements. The narrow dosage boundary between effective therapy and development of choreoathetosis suggests the same biochemical pathway is involved to a different degree. Yet, other possibilities have to be considered. For example, serotonin depletion may be a factor, since levodopa, when administered in large amounts, may depress serotonin and serotonin metabolites,[13] possibly by utilizing the decarboxylase common to both dopamine and serotonin formation.

Why do a few patients relapse after several months of pronounced improvement? Possibly another site of dopa-to-dopamine conversion, such as the brain capillary endothelium,[14] has started utilizing all of the dopa destined for the central nervous system. Possibly a relative deficiency of adenosylmethionine, a donor of the methyl groups necessary at several stages in dopamine metabolism,[15] is a factor. These questions should be answerable by animal and possibly human experimentation.

Turning again to the clinical side, we can say levodopa is an interesting and challenging drug to the physician to administer and is liable to give the parkinsonian patient significant benefit if he can reach and continue taking an adequate daily dose for the first few difficult months. From that time on, the patient usually needs no persuasion to continue the drug. We still use the principal dosage-regulating techniques and means of combating side effects noted earlier in this paper. Since no serious changes in the results of laboratory determinations have been noted, we now order routine blood studies, urinalysis, BUN and SGOT at the beginning of therapy and repeat these at three- to six-month intervals.

Since levodopa is likely to significantly help even bedridden invalids with Parkinson's disease, it seems wise to give a four- to six-month trial to most such patients. We would avoid only those incapacitated patients with a severe degree of dementia.

Patients with very mild parkinsonism of one to two years duration represent another problem. We don't yet know whether levodopa has only a suppressant action on parkinsonian symptoms or has some curative action. The latter appears unlikely, but it is a possibility. Levodopa is a troublesome medicine to take, and is still quite costly. In view of these and other factors, we have not been giving levodopa in the very mild cases unless the patient badly wants the drug and plans to continue taking it for many years to come, probably the rest of his life.

There is wide variation in patient responses to levodopa. In view of this, the physician's directions to the patient, within the confines of the dosage-regulating techniques noted above, must be very flexible. For the first year of therapy, and especially for the first few months, the physician must be readily available, willing to make suggestions over the phone, offer encouragement, make repeated minor dosage adjustments, be willing to improvise, to learn to anticipate certain of the side effects, and to see the patient promptly if indicated. These cautions should not make the physician avoid using levodopa; rather, he should approach the drug with the respect he gives to the use of other potent drugs such as dicumarol.

REFERENCES

1. Montagu KA: Catechol compounds in rat tissues and in brains of different animals. Nature (London) 180:244-245, 1957

2. Carlsson A: The occurrence, distribution and physiological role of catecholamines in the nervous system. Pharmacol Rev 11:490-493, 1959

3. Bertler A, Rosengren E: Occurrence and distribution of dopamine in brain and other tissues. Experientia 15:10-11, 1959

4. Ehringer H, Hornykiewicz O: Verteilung von Noradrenalin und Dopamin (3-Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen Systems. Klin Wschr 38:1236-1239, 1960

5. Barbeau A, Murphy GF, Sourkes TL: Excretion of dopamine in diseases of basal ganglia. Science 133:1706-1707, 1961

6. Hillarp N-A, Fuxe K, Dahlström A: Central monoamine neurons, *In* von Euler US, Rosell S, Urnäs B (Eds): Mechanisms of Release of Biogenic Amines. Oxford, Pergamon Press, 1966, pp 31-57

7. Birkmayer W, Hornykiewicz O: Der L-3, 4-Dioxyphenyl-alanine (DOPA)-Effect bei der Parkinson-Akinese. Wien Klin Wschr 73:787-788, 1961

8. Cotzias GC, Van Woert MH, Schiffer LM: Aromatic amino acids and modification of parkinsonism. New Eng J Med 276:374-379, 1967

9. Cotzias GC, Papavasiliou PS, Gellene R: Modification of parkinsonism—Chronic treatment with L-DOPA. New Eng J Med 280:337-345, 1969

10. Yahr MD, Duvoisin RC, Hoehn MM, et al: L-DOPA (L-3, 4-dihydroxyphenylanine)—Its clinical effects in parkinsonism. Trans Am Neurol Assoc 93:56-63, 1968

11. McDowell F, Lee JE, Swift T, et al: Treatment of Parkinson's syndrome with L-dihydroxyphenylalanine (levodopa). Ann Int Med 72(1):29-35, Jan. 1970

12. Birkmayer W: Failures in L-DOPA therapy, *In* Barbeau A, McDowell FH (Eds): L-DOPA and *Parkinsonism*. Philadelphia, FA Davis Co, 1970, pp 12-16

13. Van Woert MH, Bowers MD: Homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5 HIAA) during L-DOPA therapy of Parkinson's disease. Abstract. Neurol 20:377, 1970

14. Bertler A, Falck B, Rosengren E: Direct demonstration of a barrier mechanism in the brain capillaries. Acta Pharmacol (Kobenhavn) 20:317-321, 1963

15. Wurtman RJ, Rose CM, Matthysse S, et al: L-dihydroxyphenylalanine: Effect on S-adenosylmethionine in brain. Science 169:395-397, 1970